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Chapter 4: Rheumatoid Arthritis

INTRODUCTION

- *Rheumatoid arthritis* (RA) is a chronic, progressive autoimmune disease that primarily affects joints and the synovium but with possible systemic effects.

CLINICAL PRESENTATION

- Nonspecific prodromal symptoms developing over weeks to months include fatigue, weakness, low-grade fever, anorexia, and joint pain. Stiffness and myalgias may precede synovitis.
- Joint involvement is typically symmetric, affecting small joints of the hands, feet, wrists, and ankles; elbows, knees, shoulders, hips, cervical spine, and temporomandibular joints may also be involved.
- Morning stiffness usually lasts over 30 minutes and can persist all day.
- On examination, joint swelling may be visible or detectable by palpation. Affected tissue is soft, spongy, warm, and possibly erythematous. Untreated, chronic inflammation may lead to bony erosions and subluxations of wrists, metacarpophalangeal joints, and proximal interphalangeal joints (swan neck deformity, boutonnière deformity, and ulnar deviation).
- Extra-articular manifestations may include rheumatoid nodules, interstitial lung disease, pleural effusions, vasculitis, ocular issues, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.
- Rheumatoid factor (RF) is found in 70%–80% of patients; higher titers often indicate more severe disease. Anti-citrullinated protein antibodies (ACPAs) are more specific, may appear early, and predict a more aggressive course. Antinuclear antibody is positive in 25% of patients. Elevated erythrocyte sedimentation rate and C-reactive protein reflect nonspecific inflammation. Normocytic anemia, thrombocytosis or thrombocytopenia, and leukopenia may occur. Synovial fluid analysis typically shows a high white blood cell count without crystals or infection.
- Early radiologic findings include soft tissue swelling and periarticular osteoporosis. As the disease progresses, joint space narrowing, erosions, subluxations, and deformities may develop.

DIAGNOSIS

- The 2010 diagnostic criteria for RA, revised by the American College of Rheumatology (ACR) and the European League Against Rheumatism, aim to identify early disease and enable prompt treatment to prevent joint damage. Patients with synovitis in at least one joint, with no other explanation, are eligible for evaluation. A scoring system is used, and a total score of 6 or more out of 10 indicates definite RA.

TREATMENT

- Goals of Treatment: The primary goal is to achieve complete remission or low disease activity ("treat to target"). Additional goals include reducing inflammation and symptoms, preserving daily function, slowing joint damage, and delaying disability.

NONPHARMACOLOGIC THERAPY

- Patient education on the disease and medications (eg, side effects, self-injection techniques) is essential.

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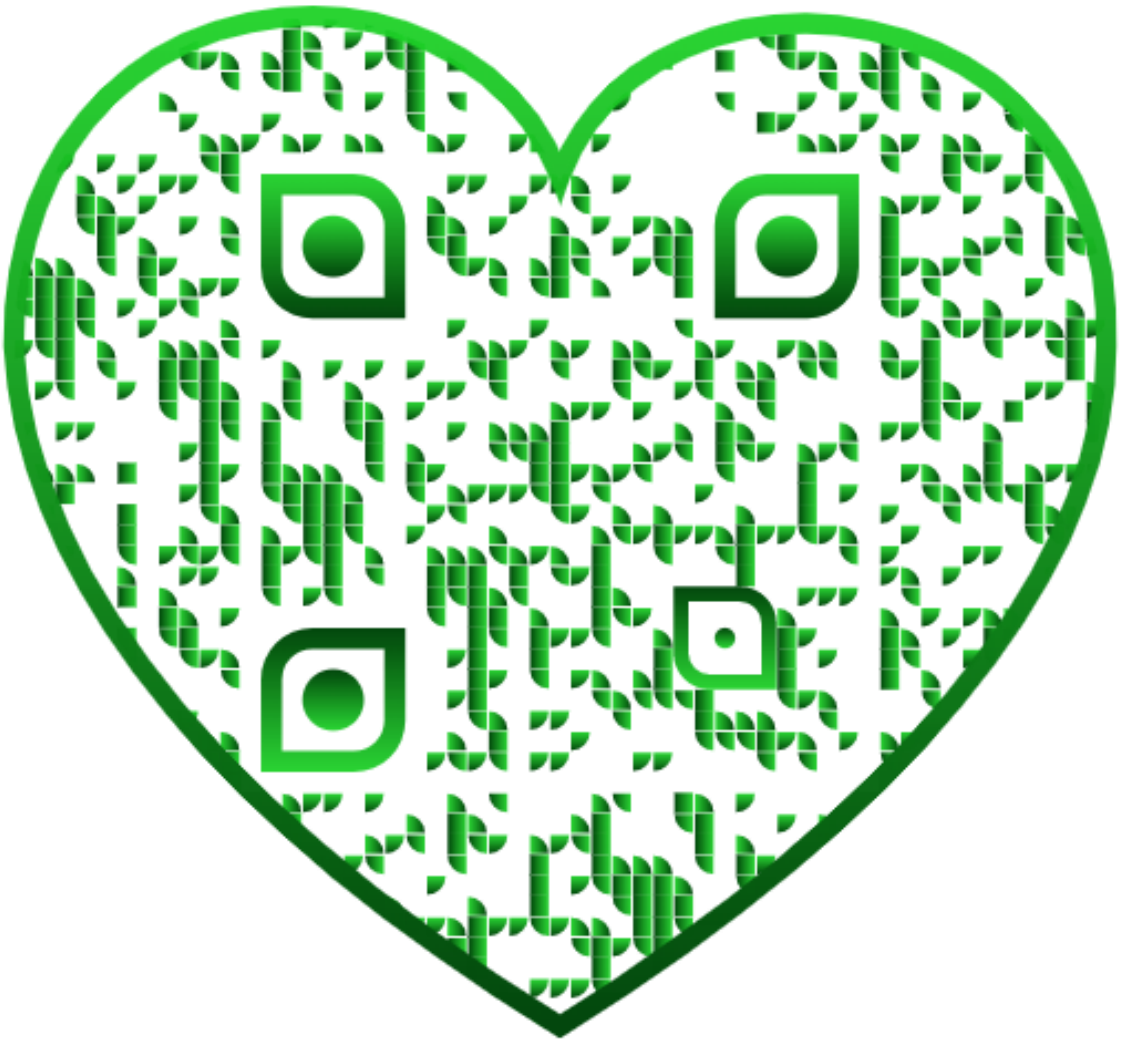

- Physical therapy helps reduce pain and inflammation while maintaining joint function. Regular physical activity—including aerobic and strength training—can improve outcomes.
- Assistive devices and orthoses (eg, braces, splints, compression, and taping) can relieve pain and enhance function. Occupational therapy offers additional support, such as footwear recommendations and splinting.
- Weight loss reduces joint stress.
- Surgical options, like joint replacement, are reserved for advanced cases with significant cartilage loss.
- Alternative therapies, including acupuncture, massage, and thermal modalities (eg, heat, cryotherapy), may also relieve pain and improve function.

PHARMACOLOGIC THERAPY

General Approach

- Therapies to treat RA and slow disease progression include disease-modifying antirheumatic drugs (DMARDs) which is categorized into conventional synthetic, targeted synthetic, and biologic DMARDs.

  ✓ Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) include **methotrexate, leflunomide, sulfasalazine,** and **hydroxychloroquine**.

  ✓ Biologic disease-modifying antirheumatic drugs (bDMARDs) include tumor necrosis factor (TNF) inhibitors (**adalimumab, certolizumab pegol**, **etanercept, golimumab,** and **infliximab)** and non-TNF inhibitor biologics (**abatacept, sarilumab, tocilizumab,** and **rituximab).**

  ✓ **Tofacitinib**, **baricitinib,** and **upadacitinib** are oral targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) that are also janus kinase (JAK) inhibitors.

- DMARD therapy should begin promptly after RA diagnosis. The 2021 ACR guidelines outline treatment based on disease activity, safety, comorbidities, and structural damage progression (**Fig. 4-1**).
- According to the guidelines, DMARD choice in treatment-naïve patients depends on disease activity. For moderate-to-high activity, methotrexate monotherapy is strongly recommended as first-line. For low disease activity, hydroxychloroquine is preferred over other csDMARDs.
- Systematic glucocorticoid prescribing at csDMARD initiation is not recommended. However, short-term use may be needed for symptom control, as DMARDs can take weeks to months to work. If used, prescribe the lowest effective dose for the shortest time. Nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen can also relieve symptoms but carry potential side effects.
- For patients treated with csDMARDs but methotrexate-naïve and with moderate-to-high disease activity, methotrexate monotherapy is preferred over combining it with a bDMARD or tsDMARD. If methotrexate fails to achieve the target, adding a bDMARD or tsDMARD is recommended over triple csDMARD therapy. For patients on a bDMARD or tsDMARD who are not at target, consider switching to a different class.
- For patients in remission or with low disease activity for at least 6 months, continuing all DMARDs is recommended over dose reduction or discontinuation. If discontinuation is the goal, taper gradually. In those not meeting treatment targets, poor prognostic factors may guide next steps. These include moderate-to-high disease activity despite csDMARDs, elevated acute phase reactants, high swollen joint count, rheumatoid factor and/or ACPA positivity, early erosions, and failure of two or more csDMARDs.
- In the absence of poor prognostic factors, other csDMARDs may be used. If poor prognostic factors are present, add a bDMARD to the csDMARD. JAK inhibitors may be considered, factoring in cardiovascular and malignancy risks. If both bDMARDs and tsDMARDs have failed, switching to another agent from either class is an option.
- Monitor patients with active disease every 1 to 3 months. If there is no improvement by 3 months or the treatment target is not met by 6 months, adjust therapy. In patients off glucocorticoids and in sustained remission, DMARD dose reduction may be considered.
- See **Tables 4-1** and **4-2** for usual dosages, adverse reactions, and monitoring parameters for medications used to treat RA.

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TABLE 4-1

Usual Doses for Disease-Modifying Antirheumatic Drugs

Drugs	Brand Names	Routes of Administration	Starting Dose	Usual Ranges or Maintenance Dose	Comments
Conventional DMARDs					
Methotrexate	Rasuvo Trexall Otrexup (SC)	Oral, SC, IM	Oral: 7.5–15 mg once weekly SC/IM: 7.5–15 mg once weekly	7.5–25 mg once weekly	Give with folic acid 1–5 mg/day to reduce adverse reactions
Leflunomide	Arava	Oral	Loading dose: 100 mg daily for 3 days, then 20 mg daily or 10–20 mg daily without loading dose	10–20 mg daily	Not recommended in liver disease (ALT >3 times ULN)
Hydroxychloroquine	Plaquenil	Oral	200 mg twice daily or 400 mg daily	200 mg twice daily or 400 mg daily	Take with food or milk; use with caution in renal or hepatic impairment
Sulfasalazine	Azulfidine	Oral	500 mg once or twice daily	1000 mg twice daily (maximum 3000 mg/day if inadequate response after 12 weeks of 2000 mg/day)	Not recommended in renal or hepatic impairment
Tumor Necrosis Factor Inhibitors					
Adalimumab	Humira	SC	40 mg every 2 weeks	40 mg every 2 weeks (may increase to 40 mg once weekly or 80 mg every other week in select patients)	
Certolizumab pegol	Cimzia	SC	400 mg at 0, 2, and 4 weeks	200 mg every other week or 400 mg every 4 weeks	
Etanercept	Enbrel	SC	50 mg once weekly or 25 mg twice weekly	Same as starting dose	
Golimumab	Simponi	SC	50 mg once monthly	Same as starting dose	
Infliximab	Remicade	IV	3 mg/kg at 0, 2, and 6 weeks, and then every 8 weeks	3–10 mg/kg every 4–8 weeks	Give in combination with methotrexate; pretreat with methylprednisolone, acetaminophen, and antihistamine
Costimulation Modulator					

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Abatacept	Orencia	IV, SC	IV: <60 kg: 500 mg, 60–100 kg: 750 mg, >100 kg: 1000 mg at 0, 2, and 4 weeks or initial IV dose followed by 125 mg SC within 24 hours SC: 125 mg weekly	IV: dose based on weight every 4 weeks SC: 125 mg weekly	
IL-6 Receptor Antagonists					
Sarilumab	Kevzara	SC	200 mg every 2 weeks	Same as starting dose	
Tocilizumab	Actemra	IV, SC	IV: 4 mg/kg every 4 weeks, SC: <100 kg: 162 mg every other week, >100 kg: 162 mg weekly	IV: 4–8 mg/kg every 4 weeks (maximum 800 mg per infusion) SC: <100 kg: 162 mg every other week, followed by an increase to weekly injections if needed; >100 kg: 162 mg weekly	Can increase the metabolism of CYP3A4 substrates
Janus Kinase Inhibitors					
Baricitinib	Olumiant	Oral IR	2 mg once daily	Same as starting dose	1 mg once daily in patients taking strong OAT3 inhibitors eGFR 30–60 mL/min/1.73 m^2: 1 mg daily; use is contraindicated with eGFR <30 mL/min/1.73 m^2; use is not recommended in severe hepatic impairment
Tofacitinib	Xeljanz	Oral	IR: 5 mg twice daily ER: 11 mg daily	Same as starting dose	5 mg once daily in moderate-to-severe renal insufficiency, moderate hepatic impairment, or concomitant CYP3A4 or CYP2C19 inhibitors; not recommended in severe hepatic impairment
Upadacitinib	Rinvoq	Oral ER	15 mg once daily	Same as starting dose	Use with caution with strong CYP3A4 inhibitors; coadministration with strong CYP3A4 inducers is not recommended; use is not recommended in severe hepatic impairment
Anti-CD20 Monoclonal Antibody					
Rituximab	Rituxan	IV	1000 mg in 2 doses given 2 weeks apart	Initial dose may be repeated every 16–24 weeks based on response	Pretreat with methylprednisolone, acetaminophen, and antihistamine

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ALT, alanine transaminase; CYP, cytochrome P; ER, extended release; IM, intramuscular; IR, immediate release; IV, intravenous; SC, subcutaneous; ULN, upper limit of normal.

TABLE 4-2

Adverse Drug Reactions and Monitoring Recommended for Medications Used in RA Treatment

Drugs	Adverse Drug Reactions	Initial Monitoring	Maintenance Monitoring
Conventional Synthetic Disease-Modifying Antirheumatic Drugs			
Methotrexate	Infection, hepatotoxicity, hepatic fibrosis, cirrhosis, elevated liver enzymes, interstitial pneumonitis, oral mucosal ulcers, rash, photosensitivity, GI perforation, diarrhea, nausea, vomiting, thrombocytopenia, leukopenia, anemia, neutropenia, cough	SCr, CBC with differential, LFTs, hepatitis B and C screening, tuberculosis screening Consider chest x-ray in patients with underlying lung disease	SCr, CBC with differential, LFTs every 2–4 weeks for 3 months after starting or following a dose increase, then every 8–12 weeks during 3–6 months of therapy, and every 12 weeks after 6 months of therapy
Leflunomide	Elevated liver enzymes, diarrhea, nausea, alopecia, elevated blood pressure, rash	CBC with differential, SCr, ALT, AST, blood pressure, tuberculosis screening	CBC with differential, SCr, ALT, AST every 2–4 weeks for 3 months after starting or following a dose increase, then every 8–12 weeks during 3–6 months of therapy, and every 12 weeks after 6 months of therapy; blood pressure periodically, signs of infection
Sulfasalazine	Rash, delayed severe hypersensitivity reactions, nausea, vomiting, diarrhea, photosensitivity, alopecia, leukopenia, anemia, thrombocytopenia, elevated liver enzymes, headache	CBC with differential, SCr, LFTs, G6PD	CBC with differential, SCr, LFTs every 2–4 weeks for 3 months after starting or following a dose increase, then every 8–12 weeks during 3–6 months of therapy, and every 12 weeks after 6 months of therapy, signs of infection, dermatologic toxicity, hypersensitivity reactions
Hydroxychloroquine	Retinal damage, rash, diarrhea, nausea, vomiting	Ophthalmologic exam (fundus examination plus visual fields and spectral-domain optical coherence tomography if maculopathy present) within 5 years of starting therapy	Ophthalmologic exam annually if risk factors for retinal damage present or annually beginning after 5 years of use if no risk factors
Biologic Disease-Modifying Antirheumatic Drugs			
Etanercept, Adalimumab, golimumab, certolizumab pegol	Local injection-site reactions, infection, malignancy, hepatotoxicity, rash, new or worsening heart failure, new or worsening demyelinating disease	Tuberculosis screening, hepatitis B and C screening, CBC with differential, CMP	Periodic skin examination, signs/symptoms of infection and malignancy, CBC with differential, and LFTs at 4 and 12 months, then every 3–6 months, neurological symptoms, heart failure symptoms

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Infliximab	Infusion-related reactions, infection, malignancy, headache, hepatotoxicity, rash, abdominal pain, new or worsening heart failure, new or worsening demyelinating disease	Tuberculosis screening, hepatitis B and C screening, CBC with differential, LFTs, CMP	CBC with differential, LFTs, signs/symptoms of infection and malignancy, neurological symptoms, heart failure symptoms
Abatacept	Headache, nausea, infusion reactions, infection, malignancy, rash	Tuberculosis screening, hepatitis B and C screening	Signs/symptoms of infection, hypersensitivity reaction, and malignancy
Tocilizumab	Local injection-site reactions, hypersensitivity reactions, infection, malignancy, GI perforation, neutropenia, thrombocytopenia, headache, hypertension, increased liver enzymes, infusion reactions, increased cholesterol	Tuberculosis screening, hepatitis B and C screening, CBC with differential, LFTs, FLP	LFTs, CBC with differential every 4–8 weeks after starting then every 3 months; FLP after 4–8 weeks of starting, then every 6 months, signs/symptoms of infection; CNS demyelinating disorders, new onset abdominal symptoms
Sarilumab	Local injection-site reactions, infection, malignancy, neutropenia, thrombocytopenia, increased liver enzymes, GI perforation, increased cholesterol, hypersensitivity reactions	Tuberculosis screening, hepatitis B screening, CBC with differential, LFTs, FLP	CBC with differential and LFTs 4–8 weeks after starting and then every 3 months, FLP 4–8 weeks after starting and every 6 months during therapy, signs/symptoms of infection, hypersensitivity reaction, and GI perforation
Rituximab	Serious, including fatal, infusion reactions, infection, malignancy, hepatitis B reactivation, mucocutaneous reactions, progressive multifocal leukoencephalopathy, bowel obstruction and perforation, CV events, blood cell disorders	Tuberculosis screening, hepatitis B and C screening, CBC with differential	CBC with differential before each treatment course and at 2- to 4-month intervals, signs/symptoms of infection
Targeted Synthetic Disease-Modifying Antirheumatic Drugs			
Tofacitinib	Infection, malignancy, GI perforations, upper respiratory tract and other infections, headache, diarrhea, nasopharyngitis, CV events, thrombosis, ILD, blood cell disorders, hyperlipidemia, hypertension	Tuberculosis screening, hepatitis B and C screening, CBC with differential, LFTs, FLP, HR, and blood pressure	CBC with differential after 4–8 weeks and every 3 months, FLP after 4–8 weeks and periodically, LFTs periodically, periodic skin examinations, HR and blood pressure, signs/symptoms of infection and malignancy
Upadacitinib	Malignancy, GI perforations, upper respiratory tract and other infections, neutropenia, lymphocytopenia, nausea, hepatotoxicity, increased liver enzymes, CV events, thrombosis, increased cholesterol	Tuberculosis screening, hepatitis B and C screening, CBC with differential, LFTs, FLP	CBC with differential, and LFTs periodically, FLP 12 weeks after therapy initiation and periodically thereafter, symptoms of thrombosis and malignancy
Baricitinib	Malignancy, upper respiratory tract herpes zoster and other infections, hepatotoxicity, increased liver enzymes, anemia, gastrointestinal perforations, thrombosis, lymphocytopenia, neutropenia, CV events, increase in SCr and CK	CBC with differential, LFTs, FLP, tuberculosis, and hepatitis B and C screening	CBC with differential, LFTs periodically, FLP 12 weeks after therapy initiation and periodically thereafter, abdominal symptoms, of thrombosis and malignancy
Other Medications			
NSAIDs	GI ulceration, bleeding, and perforation, renal damage	SCr, CBC every 2–4 weeks after starting therapy	Same as initial plus stool guaiac every 6–12 months

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Corticosteroids	Fluid retention, hyperglycemia, hypertension, behavioral and mood changes, increased appetite, weight gain, electrolyte imbalances, impaired healing, hirsutism, Cushing syndrome, HPA axis suppression, osteonecrosis of femoral and humeral heads, osteoporosis and fractures, myopathy, glaucoma, cataracts	Glucose, CBC periodically, blood pressure every 3–6 months	Same as initial

ALT, alanine aminotransferase; AST, aspartate transaminase; BP, blood pressure; CBC, complete blood count; CK, creatine kinase; CMP, comprehensive metabolic panel; CNS, central nervous system; CV, cardiovascular; FLP, fasting lipid panel; GI, gastrointestinal; Hgb, hemoglobin; HPA, hypothalamic–pituitary–adrenal; HR, heart rate; ILD, interstitial lung disease; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine.

FIGURE 4-1

Treatment algorithm for rheumatoid arthritis. (bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.)

Conventional Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs)

- **Methotrexate** inhibits dihydrofolate reductase, blocking DNA synthesis, repair, and cell replication. It is the DMARD of choice for most patients unless contraindicated. It can be used alone or with other DMARDs and has a glucocorticoid-sparing effect.

  ✓ Methotrexate is taken once weekly, usually as an oral tablet or subcutaneous (SC) injection. Oral tablets are preferred initially due to ease of use. An intramuscular (IM) form is also available but rarely used.

  ✓ Methotrexate should be given with folic acid 1 to 5 mg daily to reduce the incidence of methotrexate toxicities.

  ✓ Injectable methotrexate has greater bioavailability and superior clinical efficacy compared to oral forms, with fewer GI side effects. Patients who do not tolerate oral methotrexate may try a split oral dose over 24 hours, switch to SC injections, or increase folic acid before considering another DMARD. RA treatment doses typically range from 7.5 to 25 mg weekly. ACR guidelines recommend starting or titrating to at least 15 mg weekly within 4 to 6 weeks.

  ✓ Clinical benefit typically appears 3 to 6 weeks after starting methotrexate. Adverse effects are common (**Table 4-2**).

  ✓ Methotrexate is teratogenic—patients should use contraception and stop the drug if planning pregnancy. Methotrexate is contraindicated in pregnancy, breastfeeding, alcoholism, chronic liver disease, immunodeficiency, and hematologic disorders (eg, leukopenia, thrombocytopenia). Reduced renal function can impair excretion, requiring dose adjustment or discontinuation.

- **Leflunomide** inhibits pyrimidine synthesis; it reduces signs and symptoms of RA, inhibits structural damage, and improves physical function. It can be used as monotherapy or in combination with other DMARDs.

  ✓ The typical maintenance dose is 20 mg daily; reduce to 10 mg daily if higher doses aren't tolerated. A 100-mg daily loading dose for 3 days may speed up steady state but can increase toxicity risk.

  ✓ Adverse effects are shown in **Table 4-2**. Leflunomide is teratogenic and should not be used in patients with severe hepatic impairment.

- **Sulfasalazine** has immunomodulatory and anti-inflammatory effects. It can be used alone or with other DMARDs.

  ✓ The usual starting dose is 500 mg daily or 1 g daily in two divided doses, increased by 500 mg weekly to a maintenance dose of 2 g daily in two doses to reduce adverse events.

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✓ Clinical benefit typically appears within 4 weeks, though some may need up to 12 weeks. If the response is inadequate at 12 weeks, the dose may be increased to 3 g/day in divided doses.

✓ Use with caution in renal impairment; contraindicated in sulfonamide or salicylate allergy. GI side effects (eg, diarrhea, nausea, vomiting) are common. It may also cause urine or skin discoloration.

- **Hydroxychloroquine** can be used in combination with other DMARDs or as monotherapy in mild cases.

  ✓ The typical dose is 400 mg daily either as one dose or as two divided doses. Clinical benefit is delayed and may take several weeks.

  ✓ Its main advantage is that it does not require frequent lab monitoring, because it's not typically linked to infection risk or hepatic, renal, or hematologic issues. GI side effects may be reduced by taking it with food or splitting the dose.

  ✓ Irreversible retinal damage can occur. Patients with risk factors—such as low body weight, renal, or hepatic impairment—should have a baseline eye exam, followed by annual screening after 5 years, or sooner if risk factors are present. For high-risk patients, annual exams may be started earlier without waiting 5 years (**Table 4-2**).

Biologic DMARDs

- Biologic agents are genetically engineered proteins that reduce inflammation through various mechanisms and are classified as either TNF inhibitors or non-TNF biologics.
- Biologic DMARDs increase infection risk due to immunosuppression. A tuberculin skin test or interferon-gamma release assay should be done before identifying and treating latent or active TB. Patients should also be screened for hepatitis B due to reactivation risk, and hepatitis C screening is recommended.
- Biologics may be combined with conventional DMARDs, but multiple biologics should not be used together due to additive immunosuppression. When switching biologics, the new agent should be started when the next dose of the prior one is due to reduce adverse effects. Due to immunosuppressive risks, patients should inform providers if they are being treated for an infection or planning major surgery. Treatment may need to be paused until the infection resolves or healing occurs. Live vaccines should not be given during biologic therapy.
- *Biosimilars* are biologic products shown to have no clinically meaningful differences from the Food and Drug Administration ()-approved reference biologics. They help improve access to RA treatment by offering lower-cost alternatives to originator products. Biologics with FDA-approved biosimilars include adalimumab, infliximab, and rituximab.

TNF-α Inhibitor Biologics

- TNF inhibitors block the proinflammatory cytokine TNF-α. Clinical benefit may take several weeks, with full effect in up to 3 months. They are typically used when disease activity remains moderate to high despite csDMARDs and are more expensive.
- Selection of a TNF inhibitor depends on cost and patient preference for route and dosing frequency. These agents are contraindicated in moderate-to-severe heart failure (New York Heart Association [NYHA] class III/IV) due to reports of new or worsening symptoms. They also raise the risk of serious infections, malignancies (eg, lymphoma, skin cancers), and may trigger or worsen demyelinating disorders like multiple sclerosis.
- See **Tables 4-1** and **4-2** for dosing and monitoring information.

  ✓ **Adalimumab** (Humira) binds TNF-α and blocks its interaction with p55 and p75 TNF receptors. It is available as a prefilled syringe or pen for SC injection.

  ✓ **Certolizumab pegol** (Cimzia) is a pegylated humanized Fab fragment of a TNF-α monoclonal antibody. Lacking the Fc region, it does not trigger complement activation, antibody-dependent cell-mediated cytotoxicity, or apoptosis. Pegylation delays elimination and extends half-life. Available as a prefilled syringe for SC injection.

  ✓ **Etanercept** (Enbrel) is a recombinant TNF receptor linked to the Fc fragment of human IgG1. It is available as a prefilled syringe or pen for SC injection.

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✓ **Golimumab** (Simponi) is a human monoclonal antibody targeting human TNF-α. Available as a prefilled syringe or pen for SC use and as an IV product.

✓ **Infliximab** (Remicade) is a chimeric monoclonal antibody against TNF-α, given by IV infusion. To prevent antibody formation, methotrexate should be coadministered at RA treatment doses. Premedication with an antihistamine, acetaminophen, and/or glucocorticoid can reduce infusion reactions. Infliximab plus methotrexate improves clinical response compared to methotrexate alone.

Non-TNF Inhibitor Biologics

- **Abatacept** (Orencia) inhibits T-cell activation by binding to CD80 and CD86, which blocks the interaction between T cells CD28, thus inhibiting the activation of T cells. Abatacept can be used as an alternative to methotrexate in DMARD-naïve patients with moderate to high disease activity or as adjunctive therapy in patients who have not met treatment goals despite methotrexate therapy.

  ✓ Abatacept plus methotrexate has been shown to have similar efficacy and incidence of adverse events compared to adalimumab plus methotrexate in biologic-naïve patients who had an incomplete response to methotrexate.

  ✓ Abatacept is available in a prefilled syringe or auto-injector for SC injection and as an IV infusion.

- **Tocilizumab(Actemra)** is a monoclonal antibody that blocks IL-6 from binding to its receptor. It is used for moderate-to-severe RA with csDMARDs or as monotherapy if other options are not tolerated. Available as prefilled SC syringes and IV infusion.

- **Sarilumab** (Kevzara) is an IL-6 receptor antagonist for moderate-to-severe RA in patients with inadequate response to one or more DMARDs. It can be used alone or with csDMARDs and is given as a 200 mg SC injection every 2 weeks.

- **Rituximab** (Rituxan) is a monoclonal antibody that binds the CD20 antigen on the surface of B cells. It can be used alone or with methotrexate in patients with moderate-to-severe RA who have not responded to TNF inhibitors or have a history of lymphoproliferative disorders. Patients who failed one TNF inhibitor showed greater disease activity score reductions with rituximab than with a second TNF inhibitor.

  ✓ Rituximab is given as an IV infusion—two 1000 mg doses, 2 weeks apart. B-cell recovery may take months, allowing dosing every 24 weeks. Some patients may go longer between doses, based on symptom recurrence. It should not be given more often than every 16 weeks.

  ✓ Serious, sometimes fatal, infusion reactions can occur. Premedication with IV methylprednisolone 100 mg, plus acetaminophen and an antihistamine, is recommended 30 minutes before each infusion. Hepatitis B reactivation, mucocutaneous reactions, and progressive multifocal leukoencephalopathy have been reported.

- **Anakinra** (Kineret) is an IL-1 receptor antagonist that is less effective than other biologics and is used infrequently. It is not included in current ACR treatment recommendations but may be used in moderate-to-severe RA after failure of one or more DMARDs. It can be given alone or with DMARDs other than TNF-α inhibitors.

Targeted Synthetic DMARDs: Janus-Kinase Inhibitors

- **Baricitinib** (Olumiant), **tofacitinib** (Xeljanz), and **upadacitinib** (Rinvoq) are oral, small-molecule, nonbiologic JAK inhibitors. Baricitinib is FDA-approved for adults with moderately to severely active RA who have not responded to one or more TNF inhibitors and may be used alone or with methotrexate or other csDMARDs. Tofacitinib and upadacitinib are approved for adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. They can be used as monotherapy or with methotrexate or other nonbiologic DMARDs. JAK inhibitors should not be combined with biologic DMARDs or other JAK inhibitors.

- All JAK inhibitors carry black-box warnings for serious infections, malignancies (eg, lymphoma), and thrombosis (eg, deep vein thrombosis [DVT], pulmonary embolism [PE]). Live vaccines should be avoided, and patients must be screened and treated for latent tuberculosis before starting therapy.

Nonsteroidal Anti-inflammatory Drugs

- NSAIDs inhibit prostaglandin synthesis, targeting only a small part of the inflammatory cascade. They possess both analgesic and anti-inflammatory

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properties and reduce stiffness, but they do not slow disease progression or prevent joint damage. They should not be used as monotherapy but have a more rapid onset of action than DMARDs and may be beneficial to "bridge" patients while DMARDs take effect. For more details on NSAIDs, see Chapter 115, "Osteoarthritis."

Glucocorticoids

- Glucocorticoids have anti-inflammatory and immune-modulating properties and can slow RA progression. However, due to the risk of serious, long-term adverse effects, they should not be used as monotherapy (**Table 4-2**). Use the lowest effective dose for the shortest duration. Per ACR and European Alliance of Associations for Rheumatology (EULAR), short-term use is <3 months, and low-dose is defined as prednisone ≤7.5 mg/day (or equivalent).
- Like NSAIDs, oral glucocorticoids (eg, prednisone, methylprednisolone) can be used to "bridge" patients while DMARDs take effect. They may also serve as low-dose DMARD adjuncts in refractory cases. For acute RA flares, high-dose short-term bursts can be used, followed by tapering to the lowest effective dose or discontinuing over several days.
- Long-term glucocorticoid use is limited by adverse effects, including fluid retention, hyperglycemia, hypertension, mood changes, increased appetite, weight gain, electrolyte imbalances, poor wound healing, hirsutism, Cushing syndrome, hypothalamic–pituitary–adrenal (HPA) axis suppression, osteonecrosis (femoral/humeral heads), osteoporosis, fractures, myopathy, glaucoma, and cataracts.
- To prevent withdrawal from HPA axis suppression, glucocorticoids should be tapered—especially after prolonged or high-dose use—rather than stopped abruptly.
- The IM route may benefit nonadherent patients. Depot forms (triamcinolone acetonide, triamcinolone hexacetonide, methylprednisolone acetate) offer 2 to 6 weeks of symptom control, though onset may be delayed for several days. The depot effect provides a physiologic taper, reducing risk of HPA axis suppression.
- Intra-articular injections are useful when few joints are affected but should not be repeated frequently due to the risk of accelerated cartilage loss.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess disease activity at baseline and each follow-up to monitor disease control and treatment response. Signs of improvement include reduced joint pain, swelling, and tenderness; less morning stiffness and fatigue; and better function in daily activities.
- Perform a physical exam every visit to evaluate the number of swollen and tender joints, mobility, and deformity.
- Use validated assessment tools to measure RA disease activity, such as the Clinical Disease Activity Index, Disease Activity Score, Patient Activity Scale, Routine Assessment of Patient Index Data 3, and Simplified Disease Activity Index.
- Monitor erythrocyte sedimentation rate and C-reactive protein to assess inflammation.
- Obtain baseline radiographs of hands, wrists, and forefeet, and repeat every 2 years in patients with low disease activity or remission. Imaging may be needed more often in moderate to high disease activity. If radiographic signs of progression are present (eg, osteopenia, erosions, joint space narrowing), adjust drug therapy accordingly.
- It is important to monitor and assess for clinical and laboratory adverse effects of RA medications (**Table 4-2**).

See Chapter 116, Rheumatoid Arthritis, authored by Stephanie Gruber, Bianca Harris, and Susan Hylland, for a detailed discussion of this topic.

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